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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/844,501
Filing Date: April 27, 2001
Appellant(s): WOLFFE ET AL.

Dahna S. Pasternak
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed August 29, 2005 appealing from the Office action mailed April 13, 2004.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,635,355	Grosveld et al	06-1997
5,500,356	Li et al	03-1996

6,444,421 Chung 09-2002

NEB catalog (1995), pp. 32, 46, 48, 83.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 123-128, 130, 135, 143-145 and 147-151 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grosveld et al (U.S. Patent 5,635,355).

Grosveld teaches a method of preparing nucleic acids which comprise regulatory sequences from a cell (see column 21, claim 1, line 1, for example), comprising the steps:

a) providing a cell nucleus, wherein the nucleus comprises cellular chromatin (see column 8, lines 1-17, where nucleic of HEL and PUTKO cells are used),

b) contacting the nucleus with DNAse I, wherein the DNAseI reacts with accessible regions of cellular chromatin (see column 8, lines 17-21),

c) deproteinizing the cellular chromatin to generate deproteinized DNA (see column 8, lines 22-23, treatment with proteinase K),

d) contacting the deproteinized DNA with a second enzyme to generate DNA fragments (see column 8, lines 23-25, where the DNA was recut with Asp718).

e) contacting DNA fragments of interest that contain DNAse I hypersensitive sites with a population of vectors, to permit ligation of the DNA fragments to the vectors (see column 15, lines 43-47 and column 21, lines 18-20, claim 1),

f) selecting polynucleotides comprising a DNA fragment ligated to a vector molecule (see column 15, lines 43-47 and column 21, lines 18-20, claim 1).

With regard to claim 124, Grosveld teaches the use of animal cells (see column 8, lines 1-17).

With regard to claims 125-126, Grosveld teaches the use of DNAse I (see column 8, lines 17-21).

With regard to claims 127-128, Grosveld teaches the use of a restriction enzyme (see column 8, lines 23-25).

With regard to claim 130, Grosveld teaches BamHI (see column 13, line 57).

With regard to claim 135, Grosveld teaches preparation from different cell types (see column 8, lines 1-17).

With regard to claims 143-144, Grosveld teaches detection of the hypersensitive site with a nuclei acid probe (see column 8, lines 43-47) prior to cleavage as well as with a DNAseI probe which necessarily interacts prior to cleavage (see column 8, lines 17-21).

With regard to claim 145, Grosveld teaches the use of an isolated nucleus (see column 8, lines 1-17).

With regard to claims 147-148, 150, Grosveld teaches the use of DNAseI, (see column 8, lines 17-21).

With regard to claim 149, 151, Grosveld teaches the use of restriction enzymes (see column 8, lines 23-25).

Grosveld does not exemplify the cloning of the DNAseI hypersensitive fragment formed in column 8 into a vector as taught by claim 1. However, Grosveld expressly teaches and suggests cloning of DNAseI hypersensitive site DNA fragments (see claim 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Grosveld to clone the DNAseI hypersensitive fragments identified in column 8 of Grosveld since Grosveld expressly claims "A method of obtaining a DNA fragment comprising a dominant activator sequence, comprising 1) providing a candidate DNA fragment comprising a DNase I hypersensitive site from a genetic locus containing a structural gene that is expressed in

a manner that is specific for a particular mammalian cell type; 2) ligating the fragment to an expressible gene to form a construct. (see claim 1)." So Grosveld expressly states that DNAseI hypersensitive sites, such as those identified by the method taught by Grosveld, should be ligated into a vector in claim 1. Grosveld provides the motivation in claim 1 as well, indicated that the resultant vector can be used to provide expression of a transgene that is independent of the integration site of the vector into the host cell genome. Thus, Grosveld in column 1 identifies a problem in gene therapy, which is that integration of vectors into some sites will prevent gene expression. Grosveld teaches that this problem can be solved by cloning DNAseI hypersensitive sites into cloning vectors, which sites are associated with expression independent of the integration site. Therefore, an ordinary practitioner would have been motivated to clone the DNA fragments obtained by Grosveld as DNAseI hypersensitive sites into cloning vectors since Grosveld expressly claims such cloning and since Grosveld expressly teaches that such cloning can result in integration site independent expression.

Claims 129, 131-133 and 152 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grosveld in view of NEB catalog (1995), pages 32, 46, 48 and 83.

Grosveld teaches the limitations of claims 123-128, 130, 135, 143-145 and 147-151 as discussed above. Grosveld does not teach all of the restriction enzymes, whether sticky or blunt ended, that can be used in the method, nor does Grosveld teaches formation of blunt ends after DNAse digestion.

NEB catalog teaches Sau3AI (see page 46), required for claims 129 and 152. NEB catalog also teaches EcoRV and SmaI (see pages 32 and 48). Finally, NEB catalog teaches the use of Mung bean nuclease to form blunt ends for ligation into vectors (see page 83).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Grosveld to use the equivalent enzymes and ligation methods taught by NEB catalog since the enzymes in the NEB catalog and the methods of ligation are all known equivalents of the enzymes and methods used by Grosveld, as evidenced by the NEB catalog. As MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

Claims 136-142 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grosveld in view of Li et al (U.S. Patent 5,500,356).

Grosveld teaches the limitations of claims 123-128, 130, 135, 143-145 and 147-151 as discussed above. Grosveld does not teach comparison of cells from a variety of different sources.

Li teaches isolation of nucleic acids from "a homogeneous specimen (such as cells in tissue culture, cells of the same tissue, etc.), or a heterogeneous specimen (such as a mixture of pathogen-free and pathogen-infected cells, a mixture of cells of different tissues, species, or cells of the same or different tissue at different temporal or developmental stages, etc.). The cells, if any, of these nucleic acid sources may be either prokaryotic or eukaryotic cells (such as those of animals, humans and higher plants) (see column 5, lines 42-50)."

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Grosveld to use the variety of cell types taught by Li since an ordinary practitioner using the method of Grosveld would be motivated to obtain dominant activator sequences from any naturally occurring gene system (see column 4, lines 39-45) so Grosveld would be motivated to identify such dominant activator sequences in all tissues since every tissue is a target for some genetic therapy related to a disease in that tissue and Grosveld recognizes that such therapies require that a stably inserted gene therapy vector be expressed irrespective of location within the chromosome (see column 4). So an ordinary practitioner would have been motivated to use the multiple cell types taught by Li to screen for dominant activators in order to obtain dominant activators which function in a wide variety of cell types as suggested by Grosveld (see column 4, lines 39-45).

Claims 134 and 146 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grosveld in view of Chung et al (U.S. Patent 6,444,421).

Grosveld teaches the limitations of claims 123-128, 130, 135, 143-145 and 147-151 as discussed above. Grosveld does not teach embedding the cells in agarose.

Chung teaches embedding the cells in agarose prior to enzymatic cleavage (see column 33, lines 55-57).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Grosveld to embed the cells in agarose as taught by Chung since Chung expressly teaches that "In order to minimize shearing which can produce unwanted background of cleaved sites, the genomic DNA is isolated while the cells are embedded in an agarose plug. After purification, agarose-embedded genomic DNA is digested ... (see column 33, lines 54-57)." Thus, an ordinary practitioner performing the enzymatic cleavage and cloning method of Grosveld would have been motivated to embed the nucleic in agarose in order to minimize shearing that could produce unwanted background of false positive DNAseI hypersensitive sites as expressly taught by Chung.

(10) Response to Argument

Issue

Does the intrinsic evidence provided by the express broad definition of the claim term "library" in the specification support the reasonable interpretation that the Grosveld reference teaches a "library" within the scope of the claimed invention?

Prima facie case

The basic prima facie case of obviousness in this application is based upon a

single reference, Grosveld et al. Grosveld teaches teaches each and every limitation of the invention of claim 123, with elements a) – d) of claim 123 found in column 8, lines 1-25 and elements e)-f) found in column 15, lines 43-47 and in claim 1 at column 21. (Appellant does not separately argue the dependent claims).

While the Appellant disputes the prima facie case, the Appellant does not dispute that Grosveld teaches the steps as illustrated. What Appellant does dispute is whether Grosveld meets the preamble limitation that a "library" is prepared. The conclusion of prima facie obviousness over Grosveld is supported by several distinct lines of reasoning, including the intrinsic definition of "library" in the specification, the effect of a preamble term such as "library" in claim construction, and the ability of the art to suggest the invention for reasons distinct from those of Appellant.

Broadest Reasonable Interpretation

Appellant relies heavily on the statements in Phillips v. Awh, 75 USPQ2d 1321, 1326 (Fed. Cir. 2005) that "the ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention". These arguments are fundamentally incorrect for two reasons.

First, Phillips makes it clear that "In other cases, the specification may reveal an intentional disclaimer, or disavowal, of claim scope by the inventor. In that instance as well, the inventor has dictated the correct claim scope, and the inventor's intention, as expressed in the specification, is regarded as dispositive." In the current case, there is an express definition of the term "library". The specification defines library as "As used

herein, the term "library" refers to a pool of DNA fragments that have been propagated in some type of a cloning vector (see page 46, lines 6-7)." The specification imposes no requirement that the pool of fragments differ from one another.

Second, and perhaps more importantly, the Federal Circuit recognized that "The Patent and Trademark Office ("PTO") determines the scope of claims in patent applications not solely on the basis of the claim language, but upon giving claims their broadest reasonable construction "in light of the specification as it would be interpreted by one of ordinary skill in the art." Phillips v. Awh, 75 USPQ2d 1321, 1329 (Fed. Cir. 2005). This use of broadest reasonable construction is the central issue, because the broadest reasonable construction of the term "library" does not require that the elements differ. This construction is supported by the definition in the specification which incorporates no requirement that the DNA fragments differ.

Intrinsic evidence

To interpret the meaning of a claim term such as "library", the Federal Circuit in *C.R. Bard Inc. v. U.S. Surgical Corp.,* Fed. Cir., No. 04-1135, 10/29/04 has recently noted that,

> "A long line of cases indicates that the intrinsic record is the primary source for determining claim meaning. E.g., Bell Atl. Network Servs., Inc. v. Covad Communications Group, Inc., 262 F.3d 1258, 1268 (Fed. Cir. 2001); Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996); Autogiro Co. of Am. v. United States, 384 F.2d 391, 397-98 (Ct. Cl. 1967). The intrinsic record includes the specification and the prosecution history. Masco Corp. v. United States, 303 F.3d 1316, 1324 (Fed. Cir. 2002). Under this approach to claim construction, evidence extrinsic to the patent document "can shed useful light on the

> relevant art," but is less significant than the intrinsic record in determining the "legally operative meaning of disputed claim language." Vanderlande Indus. Nederland BV v. Int'l Trade Comm'n, 366 F.3d 1311,1318 (Fed. Cir. 2004). Particularly, our caselaw suggests that extrinsic evidence cannot alter any claim meaning discernible from intrinsic evidence. See, e.g., Intel Corp. v. VIA Techs., Inc., 319 F.3d 1357, 1367 (Fed. Cir. 2003) ("When an analysis of intrinsic evidence resolves any ambiguity in a disputed claim term, it is improper to rely on extrinsic evidence to contradict the meaning so ascertained.").

The Federal Circuit has clearly and consistently supported the position that the intrinsic evidence of the specification is determinative of the meaning of claim terms. The current situation is one in which the Appellant has acted as his own lexicographer, specifically defining the term "library" in the specification. The specification defines library as "As used herein, the term "library" refers to a pool of DNA fragments that have been propagated in some type of a cloning vector (see page 46, lines 6-7)." Grosveld teaches ligation of four distinct DNAse I hypersensitive sites (HSS) on two distinct nucleic acid fragments, along with the B-globin gene and the tkneo gene into a cloning vector (see column 15, lines 43-47). Grosveld therefore uses a pool of DNA fragments in a cloning vector. Applying the broadest reasonable interpretation to this term (See MPEP 2111) indicates that there is no requirement that the library comprise different DNA fragments, only a pool of DNA fragments. One clear interpretation of "pool of DNA fragments" is multiple copies of the same fragment, which Grosveld clearly demonstrates. In fact, as noted above, the tripartite ligation of Grosveld involves a "pool" of two different fragments, not just one, which comprise DNAse I hypersensitive

sites, which is the element designed to be cloned by the method of Grosveld and the method of claim 123 (see column 15, lines 43-47).

Appellant attempts to rely upon definitions of the term "library" used in prior art references. However, the caselaw is clear that intrinsic definitions supercede even dictionary definitions. This is particularly unambiguous in situations where the Applicant served as lexicographer, as noted by the Court in *Tex. Digital Sys., Inc. v. Telegenix, Inc.*, 308 F.3d 1193, 1204 (Fed. Cir. 2002), cert. denied, 538 U.S. 1058 (2003),

> "[T]he presumption in favor of a dictionary definition [of a claim term] will be overcome where the patentee, acting as his or her own lexicographer, has clearly set forth an explicit definition of the term different from its ordinary meaning. Further, the presumption also will be rebutted if the inventor has disavowed or disclaimed scope of coverage, by using words or expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope."

This Appellant acted as his own lexicographer, specifically defined the term "library" at page 46 of the specification without including the more limited elements discussed in the prior art. Therefore, when Appellant argues for a reliance on a particular "ordinary meaning" of the term library as it is understood in the art, this argument is rebutted by the explicit definition set forth in the specification which never discusses a requirement for "different" nucleic acids. Further, the interpretation in 10/083,682 (being handled by a different examiner) is not inconsistent since it does not require that that the clones be "different" only unordered.

The intrinsic evidence of the specification strongly supports a finding that Grosveld teaches a method which prepares a "library" as interpreted based upon the express definition of the specification.

Preamble

A second issue is whether the preamble limitation of "library" constitutes a structural limitation on the method claim. The Federal Circuit noted in *Bristol-Myers Squibb Co. v. Ben Venue Laboratories Inc.*, 58 USPQ2d 1508, 1513 (Fed. Cir. 2001) that,

> "We next construe the expression "[a] method for treating a cancer patient to effect regression of a taxol-sensitive tumor, said method being associated with reduced hematologic toxicity" in the preambles of claims 5 and 8 of the '537 patent. Again, we agree with the defendants that this language is only a statement of purpose and intended result. The expression does not result in a manipulative difference in the steps of the claim."

The Federal Circuit found in *Bristol-Myers Squibb* that in order for the preamble to represent more than a "statement of purpose" or "intended result", the preamble must result in a manipulative difference in the claim steps. In two other cases which reached different results, *Rapoport v. Dement*, 254 F.3d 1053 (Fed. Cir. 2001) and *Griffin v. Bertina*, 285 F.3d 1029 (Fed. Cir. 2002), the result differs because in each of those cases, the claims would not make sense if the argued preamble limitation were excluded. See, e.g., Griffin at 1434 ("In the absence of the preamble's stated objective to diagnose thrombosis, the term "test subject"is empty language. What is one testing for, and who is a suitable subject? Similarly, without the preamble, "assaying for the presence of a point mutation" has no purpose. Obtaining nucleic acid and assaying for a point mutation alone are merely academic exercises. The preamble is thus a necessary limitation.). In this case, if the term "library" was deleted from the claim, it would not result in any manipulative difference in the claims. The claim would still make sense as

"A method for preparing regulatory DNA" with the same steps that would achieve that preparation. The regulatory DNA would still be made with the same utilities.

Library motivation

Finally, Appellant argues that Grosveld fails to teach or suggest methods involving libraries. If either of the arguments raised above are persuasive, this argument necessarily falls because Grosveld teaches the manipulative steps of the claim. However, it is not entirely correct to state that Grosveld has "absolutely no teachings (emphasis in original)(see page 14 of brief)" about libraries. When Grosveld teaches cloning of the hypersensitive sites into the cosmids at column 9, lines 5-17 and column 13, lines 56-58, Grosveld relies upon a paper that he authored, titled "The construction of cosmid libraries which can be used to transform eukaryotic cells (see column 19, lines 58-60). This citation in the patent, especially for cloning of the hypersensitive sites, evidences that Grosveld at least has some suggestion of libraries. To the extent that the problem to be solved by Grosveld is different, this does not distinguish the claimed invention if Grosveld renders the method prima facie obvious. As MPEP 2144 notes "The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant." So even if the motivation of Grosveld is different, the fact that Grosveld expressly suggests performing the manipulative steps of the invention renders the invention prima facie obvious.

Arguments

Appellant makes one particular argument which is incorrect at page 9. Appellant questions "how could multiple fragments obtained from the nucleus of a single cell all be identical?" This statement presupposes that the method requires the use of a single cell, which is not consistent with claim 123 which does not require the use of a single cell.

Appellant's argument relating to an amendment which was not entered has no particular relevance. Appellant chose to appeal the application rather than continue prosecution by filing, for example, a continuation which would have permitted further search and consideration of the amendment. Appellant therefore expressly made the choice to pursue the current, broader claims, and chose not to include the more limiting definition.

Conclusion

The conclusion of prima facie obviousness over Grosveld is supported by several distinct lines of reasoning, including the intrinsic definition of "library" in the specification, the effect of a preamble term such as "library" in claim construction, and the ability of the art to suggest the invention for reasons distinct from those of Appellant.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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